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(71)(72) Applicants and Inventors: LEE, Nancy, M. [US/US]; 1830 Funston Avenue, San Francisco, CA 94116 (US). GOLDSTEIN, Avram [US/US]; 735 Dolores Street, Stanford, CA 94305 (US).

(74) Agents: SIEBERT, J., Suzanne et al.; Majestic, Parsons, Siebert & Hsue, Suite 1450, Four Embarcadero Center, San Francisco, CA 94111-4121 (US).

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(54) Title: ANALGESIC METHOD WITH DYNORPHIN ANALOGUES TRUNCATED AT THE N-TERMINUS

(57) Abstract

Dynorphin A analogues truncated at the N-terminus are used as analgesics to relieve pain, such as painful neuropathies where the analgesic effect is not opioid. Novel, analgesic peptides that are des-(Tyr-Gly-Gly) with respect to endogenous dynorphin are also disclosed.

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ANALGESIC METHOD WITH DYNORPHIN ANALOGUES TRUNCATED AT THE N-TERMINUS

Field of the Invention:

The present invention generally relates to dynorphin A analogues, and more particularly to dynorphin A analogues truncated at the amino terminus that are useful in analgesic methods. This invention was made with government support under Grant Nos. NIDA-02643 and NIDA-06011 awarded by the National Institutes of Health. The Government has certain rights in this invention.

Background of the Invention:

Opioids are a large class of drugs, used clinically as painkillers, that include both plant-derived and synthetic alkaloids and peptides found endogenously in the mammalian brain. While the plant-derived alkaloids have been known and used for thousands of years, the endogenous opioid peptides were discovered only in the mid-1970s. These are known to comprise three distinct gene families: β-endorphin and other peptides derived from proopiomelanocortin; enkephalins, derived from proenkephalin A; and the dynorphins, derived from proenkephalin B.

Opioid compounds interact with neuronal cells and modulate physiological functions such as nociception. Thus, one of the physiological effects attributed to the opioid system is analgesia.

Endogenous opioids exist in multiple forms in the central nervous system, and include the dynorphins, which are a series of peptides derived from the precursor prodynorphin (proenkephalin B). The first of the dynorphins to be isolated was the 17 amino acid peptide having the structure shown (and designated SEQ ID NO:1), sometimes also referred to as "dynorphin A-(1-17)":

Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-
Leu-Lys-Trp-Asp-Asn-Gln (SEQ ID NO:1)

Within the last decade, various U.S. patents have described and suggested uses of dynorphin.

U.S. Patent 4,396,606, issued August 2, 1983, inventor Goldstein, described isolation of a compound (sometimes hereinafter called "dynorphin A-(1-13)") with the structure:

Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-
Leu-Lys (SEQ ID NO:2)

This fragment of the seventeen amino acid endogenous peptide was found to be substantially more active than the enkephalins and β-endorphin in a guinea pig ileum test. Compositions containing dynorphin were suggested to be analgesic by virtue of their interaction with opioid receptor sites, and administration in the same manner as other opioid agonists (e.g. morphine) was disclosed.

U.S. Patent 4,462,941, issued July 31, 1984, inventors Lee et al., described dynorphin amide analogs with ten amino acid residues. These dynorphin A-(1-10) amide analogs do not have significant analgesic activity in opioid tail flick tests (unless given in huge doses where they tend to produce convulsions).

Enkephalin analogues that are conformationally constrained by a cyclic structure (such as with a disulfide bridge) are described by U.S. Patent

4,518,711, issued May 21, 1985, inventors Hruby et al. Subsequently, dynorphin analogues have become known that have cysteine replacements at the amino acid residue 5 (usually leucine) and at the amino acid residue 11 (usually lysine). The amino acid residue 8 (usually an isoleucine) and the amino acid residue 13 (usually a lysine) have similarly been replaced by cysteines in a bridged relationship. The bridges, or cyclic structures, appear to assist in stabilizing the dynorphin analogues against *in vivo* degradations.

In an international application published under the Patent Cooperation Treaty on December 23, 1993, Lee et al. disclosed therapeutic uses of certain truncated N-terminal dynorphin A analogues in conjunction with narcotic analgesics in order to potentiate activity of the narcotic analgesic and/or to block withdrawal symptoms (International Publication No. WO93/25217). However, uses in conjunction with narcotic analgesics for opioid effects require a presence of opioid drugs.

Opioid drugs are used clinically as painkillers, but their usefulness is limited by the tolerance and dependence that normally develops upon chronic treatment. Tolerance may be defined as an increase in the amount of drug needed to achieve a certain level of analgesia, while dependence manifests itself in the need to continue taking drug to prevent withdrawal symptoms. Despite a great deal of research on these phenomena, little is known about their molecular basis. Opioid drugs, such as, for example, morphine, are addictive and have central opioid side effects such as drowsiness and impairment of mental activity.

Some non-opiat compositions have been suggested for relieving chr nic pain, such as

experienced as burning or hyperesthesia pain. Thus, U.S. Patent 5,006,510, issued April 9, 1991, inventor Ellis, describes somatostatin analogue compositions for topical administration in the treatment of pain where opiates do not significantly change the experience of the patient's pain.

Nevertheless, a variety of painful conditions exist that are relatively resistant to analgesic relief by narcotic analgesics such as morphine.

<u>Summary of the Invention</u>:

In one aspect of the present invention, peptides are used to relieve pain. The peptides have at least six, preferably have at least seven, amino acid residues, and are analogues of dynorphin A that are truncated (with respect to endogenous dynorphin) at the N-terminus, such as being des-(Tyr), des-(Tyr-Gly), or des-(Tyr-Gly-Gly) with respect to the endogenous dynorphin A. These peptides may be formulated in a pharmaceutically acceptable solution or with a pharmaceutically acceptable carrier, and are usefully administered to a patient experiencing pain.

Administration of dynorphin A analogues in practicing the invention is preferably systemic, such as intravenous, and includes transnasal, transrectal, intrathecal, intramuscular, transdermal electrotransport, or subcutaneous procedures in dose ranges of between about 50 to about 2,000 μg/kg (or by continuous infusion). Administration may also be topical (e.g. to wounds or mucus membranes) and oral administration may also be feasible.

Practice of the invention is useful generally for analgesia to counter pain, and is particularly us ful for painful conditions, often having unknown etiology, such as "n uropathic pain," "neurogenic pain,"

"hyperesthesia" (a morbid response to normal sensory stimuli perceived as extremely painful), "allodynia," "causalgia" (meaning a pathological response to nerve injury that is disabling), persistent lower back pain, visceral pain, bone pain (such as is experienced by some cancer patients), post-operative pain, and wounds such as from burns. Because practice of the invention provides non-opiate analgesia, the central nervous system side effects of a drug such as morphine (e.g. drowsiness, impaired mental functioning and the like) are avoided.

Detailed Description of the Preferred Embodiments:

The present invention concerns the interaction of dynorphin A analogues with non-opioid receptors in an analgesic manner. In particular, preferred practice of the invention pertains to use of dynorphin A analogues that are des-(Tyr), des-(Tyr-Gly), or des-(Tyr-Gly-Gly) with respect to dynorphin A.

It is known that dynorphin A-(2-17) does not bind to μ, δ, or K opioid receptors. However, we have discovered that the non-opioid binding dynorphin A analogues show substantial antinociceptive (that is, analgesic) activity, particularly when administered systemically (such as by i.v.). This potency is retained even in morphine-tolerant animals. That is, there is a lack of cross-tolerance.

At this point, we do not know the identity of the non-opioid receptors with which dynorphin A analogues are interacting. However, data obtained from *in vivo* assays used for demonstrating non-opioid analgesic activity shows that practice of the present invention is useful to relieve pain where the analgesic effect is not mediated by opioid receptors.

For example, many patients suffer from pain associated with an injury or a disease that interrupts some or all of the axons in a nerve (e.g. painful neuropathies). Following nerve injury, the regenerating tips of damaged primary afferent axons acquire abnormal properties, such as firing spontaneously and developing abnormal sensitivity to certain types of stimulation. It is believed that such axons with abnormal properties are present in other conditions such as diabetic disorders. Among the syndromes of painful peripheral neuropathies are those usually classified on the basis of an associated disease, such as phantom pain when the nerve has been amputated. These types of pain are often not relieved by or are relatively resistant to opioid analgesics.

Peptides used in practicing the invention have at least six, and preferably have seven, amino acids. In one aspect of this invention, suitable peptides can be viewed as having amino acid residues analogous to endogenous dynorphin A (SEQ ID NO:1), but the peptides used preferably are des-(Tyr), as shown by the amino acid residue sequences of SEQ ID NOS:4-12:

Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn (SEQ ID NO:4);

Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp (SEQ ID NO:5);

Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp (SEQ ID NO:6);

Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Ly s (SEQ ID NO:7);

Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu (SEQ ID NO:8);

Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys (SEQ ID NO:9);

Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro (SEQ ID NO:10);

Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg (SEQ ID NO:11); and,

Gly-Gly-Phe-Leu-Arg-Arg-Ile (SEQ ID NO:12).

We sometimes refer to the SEQ ID NOS:4-12 peptides as dynorphin A-(2-16) through dynorphin A-(2-8), respectively. Further, the variations known to the art (e.g. some of which are discussed in U.S. Patent 4,462,941) are meant to be within the scope of these suitable peptides. Yet further, in any of the SEQ ID NOS:4-12, any one or two of the residues may be replaced with the same or a different amino acid residue in the D-configuration (to increase *in vivo* stability), such as where the N-terminal Gly is replaced by D-Ala, or a modification for conformational stability or rigidity may be made, such as where a plurality of the specified amino acid residues are replaced by moieties capable of forming a cyclic structure, or bridge (e.g., the disulfide bridge). An illustrative bridged such dynorphin A analogue is where the normal leucine at the 5 position and the lysine at the 11 position (these positions referred to as though in endogenous dynorphin), are replaced by cysteines, whose disulfide bridge provides conformational stability. Any of the peptides used in practicing this invention may have the C-terminal and/or the N-terminal including a blocking group, for example, where the N-terminus has been acetylated. All the peptides can also be used in their free acid or amide form.

Des-(Tyr) peptides for this invention can also lack the next adjacent one or two glycine residues of the endogenous dynorphin A and thus b des-(Tyr-Gly) or des-(Tyr-Gly-Gly), as shown by SEQ ID NOS:13-21 and SEQ ID NOS:22-29, respectively, which can similarly be

modified to increase conformational stability or rigidity as already described for SEQ ID NOS:4-12 and where the des-(Tyr-Gly) peptides can also have the N-terminal Gly replaced by D-Ala, the C-terminus and/or the N-terminus can include a blocking group as are well known to the art (such as to retard degradation of the peptide within the body), and the peptides can be in free acid or amide form:

Des-(Tyr-Gly)

Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln (SEQ ID NO:13);

Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn (SEQ ID NO:14);

Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp (SEQ ID NO:15);

Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Tr p (SEQ ID NO:16);

Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys (SEQ ID NO:17);

Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu (SEQ ID NO:18);

Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys (SEQ ID NO:19);

Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro (SEQ ID NO:20); and

Gly-Phe-Leu-Arg-Arg-Ile-Arg (SEQ ID NO:21).

We sometimes refer to the SEQ ID NOS:13-21 peptides as dynorphin A-(3-17) through dynorphin A-(3-9), respectively.

Des-(Tyr-Gly-Gly)

Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln (SEQ ID NO:22);

Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn (SEQ ID NO:23);

Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-As p (SEQ ID NO:24);

Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp (SEQ ID NO:25);

Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys (SEQ ID NO:26);

Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu (SEQ ID NO:27);

Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys (SEQ ID NO:28); and

Phe-Leu-Arg-Arg-Ile-Arg-Pro (SEQ ID NO:29).

We sometimes refer to the SEQ ID NOS:22-29 peptides as dynorphin A-(4-17) through dynorphin A-(4-10), respectively.

The des-(Tyr) dynorphin A-(2-17) is likewise useful in practicing this invention (SEQ ID NO:30) with the variations and modifications known to the art and as earlier noted.

All the peptides suitable for practicing this invention may be readily prepared synthetically, such as by solid phase peptide synthesis techniques. When a chloromethylated resin or a hydroxymethyl resin has been used as a resin support, then the peptide cleaved from the resin support will be in the form of the carboxyl terminal benzyl ester, which may then be readily converted by methods well known in the art to provide the carboxyl terminal amide form of the peptide.

Table 1 summarizes peptides useful for analgesic, but non-opioid, properties in practicing the present invention as set out by SEQ ID NOS:22-29, and which are believed to be novel peptides.

TABLE 1

Novel Peptides With Analgesic, Non-Opioid Property	SEQ ID NO:
Dyn A-(4-17)	22
Dyn A-(4-16)	23
Dyn A-(4-15)	24
Dyn A-(4-14)	25
Dyn A-(4-13)	26
Dyn A-(4-12)	27
Dyn A-(4-11)	28
Dyn A-(4-10)	29

Researchers in the field seeking to clone cDNA encoding an opioid receptor had recently noted that a des-(Tyr) dynorphin did not compete at all in assays with various ligands (Xie et al., *Proc. Natl. Acad. Sci. USA*, *89*, pp. 4124-4128 (1992)). However, the des-(Tyr) dynorphin peptides useful in practicing this invention not only lack the N-terminal tyrosine, but indeed the des-(Tyr-Gly-Gly) dynorphin peptides summarized in Table 1 lack the first three N-terminal amino acid residues. Nevertheless, these novel peptides have substantial analgesic properties that are useful in treating pain, such as pain that is otherwise relatively resistant to opiates. Thus, the present invention is a new method of providing effective analgesia with completely non-opioid compounds. This means practice of the invention will avoid the addiction, tolerance, dependence, and central opioid side effects that are serious disadvantages in the use of opioid drugs.

Peptides of the invention are preferably formulated in a pharmaceutically acceptable solution or with a pharmaceutically acceptable carrier, and then are administered in such a solution or carrier. Depending upon th mode c administration, the peptides may thus

be formulated with a wide variety of physiologically acceptable carriers, such as aqueous saline and phosphate buffered saline, and may include physiologically acceptable excipients, such as glucose, mannitol, or the like.

Administration may be by transdermal electrotransport (sometimes also referred to as using an iontophoretic current). For example, such a means of drug administration is described by U.S. Patent 5,312,326, issued May 17, 1994, inventors Myers et al. Other assemblies that may be suitable for selective drug release are described by U.S. Patent 5,290,240, issued March 1, 1994, inventor Horres, and by U.S. Patent 5,288,289, issued February 22, 1994, inventors Haak et al.

EXPERIMENTAL

Randomly bred male ICR mice (Sasco, Omaha, Nebraska) weighing 20 to 25 g were used in all experiments. All animals were supplied food and water *ad libitum* and were housed in a temperature ($22\pm1°C$)- and humidity (40-50%)- controlled animal room for at least one day before experimentation. Each mouse was used only once.

The abdominal stretching (writhing) assay as described by Hayashi and Takemori (1971) was used as an antinociceptive assay. Mice were injected intraperitoneally with 10 ml/kg of 0.6% acetic acid, and the number of writhing responses per animal was counted for a six-minute period commencing five minutes after acetic acid injection. A writhe was defined as a wave of contraction of the abdominal musculature followed by a stretching of hind limbs. Number of writhes per animal was expressed as mean ± S.E. Antinociceptive activity

was expressed as percentage decrease in the mean number of writhes observed in the drug-treated animals compared with the mean number of writhes in the saline control group. Administration of drugs was timed so that the peak action coincided with the center of the observation period. A minimum of ten mice were used at each of three dose levels to determine the dose response curve and ED_{50} of the drug.

The parallel line assay of Finney (1964) was used to estimate ED_{50} values, 95% confidence intervals and potency ratios.

The data of the following Tables 2-4 use the terminology "AD_{50}" to indicate analgesic doses. The analgesic doses represent three data points taken from at least 30 animals (and thus are the summation from dose response curves) and represent the dose at which 50% of the animals showed an analgesic effect.

TABLE 2

Antinociceptive Response in Writhing Assay (Naive Mice)

Embodiments of the Invention	AD_{50} (µmole/kg)
Dyn A-(2-17), i.v., 5 min.	1.1 (0.99-1.20)
Dyn A-(2-17), i.v., 30 min.	1.1 (0.99-1.20)
Dyn A-(2-17), i.v., 60 min.	5.9 (5.2-7.8)
Dyn A-(2-17), i.v., 2 hrs.	16.1 (13.4-20.5)
Dyn A-(2-17), i.v., 5 min. + Nal, s.c., 50 µmole/kg	1.8 (1.7-1.9)
Dyn A-(2-17), i.t., 5 min.	5.1 (4.0-6.4) nmole/mouse
Dyn A-(2-17), i.c.v., 5 min.	7.3 (6.9-7.8) nmole/mouse
Dyn A-(2-17), i.p., 5 min.	3.1 (2-5)
Dyn A-(2-12), i.v., 5 min.	3.8 (2.5-5.4)
Dyn A-(3-17), i.v., 5 min.	2.4 (1.6-3.7)
Dyn A-(3-13), i.v., 5 min.	7.5 (4.8-11.5)
Dyn A-(4-17), i.v., 5 min.	5.7 (3.6-8.80)
Comparative	
Dyn A-(7-17), i.v., 5 min.	>100

As seen from the data of Table 2, dynorphin A-(2-17), when administered i.v. at 1.1 µmole/kg of animal weight, was an analgesic dose for 50% of the animals tested despite the animals being subjected to an injection five minutes later with acetic acid and then judged by the writhing assay. Calculations show that the amounts administered of dynorphin A analogues (which are basic compounds) are insufficient to neutralize even 1% of the acidity of the administ red acetic acid, and thus the ffects shown from the writhing assay are not

due to a simple chemical neutralization. As further seen by the data of Table 2, the duration of action was substantially the same when administered 30 minutes before the acetic acid, although at 60 minutes one sees the analgesic property begins to decline in duration of action.

Still with reference to the data of Table 2, the non-opioid effect of the analgesia being measured is indicated by the fact that when naloxone (50 μmole/kg) is administered in conjunction with dynorphin A-(2-17), substantially equivalent analgesic properties are still obtained. Naloxone, of course, is an antagonist of opioid receptors, and thus this data shows the analgesic effect is not being mediated through opioid receptors. The amount of naloxone administered was more than sufficient for antagonism of opioid analgesia, both with morphine and U50,488H which act primarily at μ and K opioid receptors, respectively, as shown by Table 3. Still with reference to the data of Table 2, one sees that the peptide dynorphin A-(4-17), even though it is missing the first three amino acid residues of dynorphin A-(1-17), continued to provide good analgesia. However, by contrast, dynorphin A-(7-17), did not.

TABLE 3

Comparative	AD_{50} (μmole/kg)
U50,488H, i.v., 30 min.	2.0 (1.9-2.2)
U50,488H, + Nal., 10 μmole/kg	17.2 (14.9-19.9)
Morphine, s.c., 30 min.	2.6 (2.1-3.2)
Morphine + Nal., 10 μmole/kg	23.0 (15-35)

The data of Table 4 wer collected from morphine tolerant mice (where th mice were made tol rant to morphine by implantation of a 75 mg pellet

according to standard procedures), and these data show that the morphine-tolerant animals are not cross-tolerant to the des-(Tyr) dynorphin A analogue.

TABLE 4

Antinociceptive Response
in Writhing Assay (Morphine-Tolerant Mice)

	AD_{50} (μmole/kg)
Dyn A-(2-17), i.v., 5 min. (one morphine pellet for 3 days)	2.2 (1.5-3.1)
Dyn A-(2-17), i.v., 5 min. (one morphine pellet for 5 days)	1.9 (1.1-3.2)

In conclusion, practice of the invention provides a non-opioid analgesia, where the anti-nociception is likely not an effect on the central nervous system.

It is to be understood that while the invention has been described above in conjunction with preferred specific embodiments, the description and examples are intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims.

It is Claimed:

1. A method for inducing analgesia in a patient experiencing chronic pain comprising:

administering to the patient a dynorphin A analogue, the analogue being truncated at the N-terminus, in an amount sufficient to induce analgesia.

2. The method as in claim 1 wherein the dynorphin A analogue is in acid or amide form.

3. The method as in claim 2 wherein the dynorphin A analogue has seven or more amino acid residues.

4. The method as in claim 3 wherein the dynorphin A analogue is des-(Tyr) at the N-terminus.

5. The method as in claim 3 wherein the dynorphin A analogue is des-(Tyr-Gly) at the N-terminus.

6. The method as in claim 3 wherein the dynorphin A analogue is des-(Tyr-Gly-Gly) at the N-terminus.

7. The method as in claim 3 or 4 wherein the N-terminal glycine has been replaced by D-Ala.

8. The method as in claim 1 wherein the dynorphin A analogue includes a blocking group at the C-terminus and/or at the N-terminus.

9. The method as in claim 1 wherein administration is intravenous, transnasal, transrectal,

intrathecal, intramuscular, topical, oral, or subcutaneous or is by transdermal electrotransport.

10. A method for relieving pain in a patient experiencing pain resistant to opioid analgesics comprising:

administering a dynorphin A analogue that is des-(Tyr), des-(Tyr-Gly), or des-(Tyr-Gly-Gly) in acid or amide form and that has seven to sixteen amino acid residues.

11. The method as in claim 10 wherein the dynorphin A analogue is administered in a dose of at least about 50 μg/kg patient body weight.

12. The method as in claim 10 or 11 wherein the dose is by intravenous, transnasal, transrectal, intrathecal, intramuscular, transdermal electrotransport, topical, oral, or subcutaneous administration

13. A peptide having an analgesic property with the structure:

Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln (SEQ ID NO:22);

Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn (SEQ ID NO:23);

Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp (SEQ ID NO:24);

Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp (SEQ ID NO:25);

Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys (SEQ ID NO:26);

Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu (SEQ ID NO:27);

Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys (SEQ ID NO:28); or

Phe-L u-Arg-Arg-Ile-Arg-Pro (SEQ ID NO:29),

where the N-terminus and/or the C-terminus can include a blocking group.

14. The peptide as in claim 13 being in acid or amide form.

15. The peptide as in claim 13 wherein two or more cysteines replace one or more leucine, lysine, or isoleucine amino acid residues.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/09563

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 38/00; C07K 7/00, 7/06 7/08
US CL : 530/327, 328, 329; 514/14, 15, 16
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/327, 328, 329; 514/14, 15, 16

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, Cas Online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,361,553 (LOH ET AL.) 30 November 1982, see entire document.	1-15
Y	US, A, 4,462,941 (LEE ET AL.) 31 July 1984, see entire document.	1-15
Y	US, A, 4,396,606 (GOLDSTEIN) 02 August 1983, see entire document.	1-15

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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Date of the actual completion of the international search

26 NOVEMBER 1994

Date of mailing of the international search report

20 DEC 1994

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
S.G. Marshall
Jill Warden for
Telephone No. (703) 308-0196

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	The Journal of Pharmacology and Experimental Therapeutics, Vol. 266, No. 1, issued 1993, Takemori et al., "Suppression by Dynorphin A and [DesTyr] Dynorphin A Peptides of the Expression of Opiate Withdrawal and Tolerance in Morphine-Dependent Mice", pages 121-124, see entire document.	1-15